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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,729	06/12/2001	Jay M. Short	09010-003005	6449

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/880,729	SHORT ET AL.
	Examiner	Art Unit
	Manjunath N. Rao, Ph.D.	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 9-26-03, 10-8-03.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 42-54 and 93-110 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 42-54,93-101 and 104-110 is/are rejected.

7)☒ Claim(s) 102 and 103 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 12 June 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8-20-02 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 42-54, 93-110 are currently pending and present for examination in this application.

Applicants' amendments and arguments filed on 9-26-03 and 10-8-03, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the objections to the specification and rejection of claims under 35 U.S.C. 112, 2nd paragraph and the obviousness rejection under 35 U.S.C. 103(a) in view of claim amendments.

Priority

Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 08/518,615 filed on 08/23/1995, now US 5,962,258, 0/951,889 filed on 10/16/1997, now US 6,008,032, 09/472,857 filed on 12/27/1999, now US 6,245,647. However, Examiner has not granted the above priority dates for claims 43-55 as they do not support in the priority documents.

In response to the previous Office action not granting the priority to previously filed applications, applicants have responded by reciting paragraphs from parent applications and arguing that said recitations provide support for the instant application. However, it can be readily seen that none of those paragraphs recite the structural features of the polynucleotides encompassed in the claims of the instant application. The paragraphs recited from parent applications only provide a generalized support but not specific support for the claims in the

instant application. Therefore, Examiner has not granted the above priority dates for claims 43-55 as they do not support in the priority documents.

Claim Objections

Claim 109 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 42 (overlooking the preamble). When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 109 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 109 appears to be drawn to a method of generating a carboxy methyl cellulase (enzyme). However, the steps recited further lead to the generation of a variant polynucleotide encoding a carboxymethyl cellulase but not the polypeptide, rendering the claim indefinite. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-54, 93-101, 104-110 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method for generating a variant comprising providing (1) a genus of polynucleotides encoding a carboxymethyl cellulase and having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% sequence identity to the polynucleotide with SEQ ID NO: 1, (2) a genus of polynucleotides encoding a carboxymethyl cellulase and comprising at least 30, 50, 75, 100, 150 or 200 consecutive nucleotides of a polynucleotide sequence having at least 50% sequence identity to the polynucleotide with SEQ ID NO: 1, (3) a genus of polynucleotides encoding the carboxymethyl cellulase that hybridizes to SEQ ID NO:1 under stringent conditions or polynucleotide sequences that are complementary to all the above. While the specification is enabled for a the polynucleotide of SEQ ID NO: 1 and the corresponding encoded polypeptide, as well as for a method for generating polynucleotide variants --of SEQ ID NO: 1 or a polynucleotide that is 97% identical to SEQ ID NO:1 or polynucleotides encoding carboxymethyl cellulase and capable of hybridizing to SEQ ID NO:1 under highly stringent conditions-- which still retain the activity of encoding the polypeptide with cellulase activity, does not reasonably provide enablement for a method of generating a variant polynucleotide encoding carboxymethyl cellulase as claimed specifically in claims 42, 108 and 109 using (1) a genus of polynucleotides encoding a carboxymethyl cellulase and

having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% sequence identity to the polynucleotide with SEQ ID NO: 1, (2) a genus of polynucleotides encoding a carboxymethyl cellulase and comprising at least 30, 50, 75, 100, 150 or 200 consecutive nucleotides of a polynucleotide sequence having at least 50% sequence identity to the polynucleotide with SEQ ID NO: 1.

It is noted that the term "variant" has been defined in the specification (page 13-14) as "polynucleotide or polypeptide modified at one or more base pairs, codons, introns, exons, or amino acid residues yet still retain the biological activity of a CMC-cellulase". The specification does not disclose the critical structural elements required in a nucleic acid having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1 to encode a polypeptide which has CMC-cellulase activity. The specification does not also disclose the critical structural elements required in a polynucleotide comprising at least 30, 50, 75, 100, 150 or 200 consecutive nucleotides of a polynucleotide sequence having at least 50% sequence identity to the polynucleotide with SEQ ID NO: 1.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

While one could argue that the nucleic acids required to practice the claimed method are adequately described since one can isolate nucleic acids of similar function by sequence

comparison using the polynucleotides/polypeptides of the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine function and that small structural changes can drastically change function. Bork (Genome Research, 10:398-400, 2000;) teaches protein function is context dependent, and both molecular and cellular aspects must be considered. Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995; cited in the IDS) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998; cited in the IDS) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a single species of the genera of nucleic acids required to practice the invention which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed method.

The scope of the claims as described above is not commensurate with the enablement provided in regard to the large number of unknown polynucleotides required to practice the claimed method. As indicated above, based on the support provided in the specification, claims are enabled for a method of generating variants --of the polynucleotide with SEQ ID NO: 1 or

polynucleotides encoding carboxymethyl cellulase and having 97% sequence identity with SEQ ID NO:1 or polynucleotides encoding carboxymethyl cellulase and capable of hybridizing to SEQ ID NO:1 under highly stringent conditions-- which still retain CMC-cellulase activity. However the specification fails to disclose a method of creating variants, using a broad set of polynucleotides such as (1) a genus of polynucleotides encoding a carboxymethyl cellulase and having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% sequence identity to the polynucleotide with SEQ ID NO: 1, (2) a genus of polynucleotides encoding a carboxymethyl cellulase and comprising at least 30, 50, 75, 100, 150 or 200 consecutive nucleotides of a polynucleotide sequence having at least 50% sequence identity to the polynucleotide with SEQ ID NO: 1. The specification neither provides the starting polynucleotides encompassed in the claims nor guidance for identifying said genus of polynucleotides which are required before the first step of the method. Therefore without the provision of the polynucleotides required for the method, the method is non-enabled. Furthermore, as discussed above, the state of the art teaches that isolation of polynucleotides of similar function is unpredictable, as evidenced by Bork, Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. Since structure determines function, one of skill in the art would require some knowledge or guidance as to how structure correlates with function to isolate the polynucleotides required to practice the claimed method. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to first

screen and isolate those polynucleotides as encompassed by the claims and next, to practice the claimed method using such polynucleotides.

Furthermore, claim 110 is not further enabled because it lacks the step of selecting those polynucleotides that continue to have the activity of encoding a polypeptide with CMC-cellulase activity.

Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

In response to the previous Office action applicants have traversed the above rejection arguing that the invention is sufficiently enabled. In responding to the rejection, applicant takes the support of the Declaration filed under rule 1.132 by Dr. Short. In summary applicants argue that the experimentation required for practicing the claimed method is routine and while the quantity of experimentation necessary may be more it is not undue in view of the skills developed in the art. Applicants also argue that amending the claims have overcome the first part of the enablement rejection as well.

While Examiner agrees that claim amendments have indeed overcome the first part of the previously held rejection, he respectfully disagrees with the applicants that the experimentation required to arrive at polynucleotides needed for practice of the claimed method is not undue. Applicant's argument is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants for the method as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the

infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. Hence the above rejection is maintained.

Claims 42-54, 93-101, 104-110 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method for generating a variant comprising obtaining (1) a genus of polynucleotides encoding a CMC cellulase and having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% sequence identity to the polynucleotide with SEQ ID NO: 1, a genus of polynucleotides encoding a carboxymethyl cellulase and comprising at least 30, 50, 75, 100, 150 or 200 consecutive nucleotides of the above polynucleotide sequences. While the specification describes the polynucleotide of SEQ ID NO: 1 and the corresponding polypeptide, as well as a method for generating polynucleotide/polypeptide variants of the polynucleotide/polypeptide of SEQ ID NO: 1 which still retain cellulase activity, the specification fails to describe the above polynucleotides required for the claimed methods.

While one could argue that the nucleic acids required to practice the claimed method are adequately described since one can isolate nucleic acids of similar function by sequence comparison using the polynucleotides/polypeptides of the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine function and that small structural changes can drastically change function. Bork (Genome Research, 10:398-400, 2000;) teaches protein function is context dependent, and both molecular and cellular aspects must be considered. Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995; cited in the IDS) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998; cited in the IDS) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a single species of the genera of nucleic acids required to practice the invention.

The specification does not contain any disclosure of the structure of all nucleic acid sequences included in the genera required for practicing the claimed method. The genus of nucleic acids required is a large variable genus. A sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by

nucleotide sequence or a recitation of structural features common to members of the genus, **which features constitute a substantial portion of the genus**. The recited structural feature of the genus (i.e., a genus of polynucleotides encoding a carboxymethyl cellulase and comprising at least 30, 50, 75, 100, 150 or 200 consecutive nucleotides of polynucleotide sequences having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% sequence identity to the polynucleotide with SEQ ID NO: 1) does not constitute a substantial portion of the genus as the remainder of the structure of any nucleic acid encoding a polypeptide having cellulase activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action applicants have traversed the above rejection arguing that the invention is sufficiently described so that one skilled in the art can indeed reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicants argue at length, that according to the Guidelines, they have described the genus in terms of its physico-chemical properties (i.e., % sequence identity of SEQ ID NO:1 and 2) and function (i.e., encoding a CMC-cellulase) and therefore meeting the requirement of written description. While Examiner agrees that indeed applicants have described polynucleotides required for the method by providing the structure and function, the

extent of description provided for claims such as claim 42 and other which require the use of polynucleotides encoding CMC-cellulase and comprising 30, 50, 75 etc. nucleotides of polynucleotides that are 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% identical to SEQ ID NO;1 is insufficient or non-existent. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient features that constitute a substantial portion of the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of at least a substantial portion of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one or few or partial features within the genus. In the instant case the polynucleotides required for the claimed method includes species that have been described with very little description (i.e., comprising **30, 50, 75 etc.** nucleotides of polynucleotides that are 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% identical to SEQ ID NO;1). As such, neither the

description of the structure and function of SEQ ID NO:1 nor the disclosure solely of incomplete or highly partial structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Therefore the above rejection is maintained.

Conclusion

None of the claims are allowable. Claims 102-103 are objected.

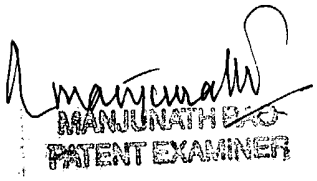
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
January 14, 2004